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VIA ECF

The Honorable Renée Marie Bumb
United States District Court Judge
District of New Jersey
Mitchell H. Cohen Building & U.S. Courthouse
4th & Cooper Streets, Room 1050
Camden, NJ 08101

Re: *In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation*., U.S. District Court for the District of New Jersey; Case No. 1:19-md-02875

Dear Judge Bumb:

Defendants submit this letter in response to the Court's invitation to provide a summary of the anticipated testimony of Defendants' joint expert, acclaimed cancer biology researcher and physician Lewis Chodosh, M.D., Ph.D., which rebuts Plaintiffs' argument that valsartan containing NDMA or NDEA at the levels at issue posed an unacceptable risk and therefore rendered the medications worthless. (*See* 9/17/24 Hr'g Tr. 134:19-135:8.) During the July 23 hearing, the Court ruled that Defendants "can present studies that say that small doses don't present an unacceptable risk." (*See* 7/23/24 Hr'g Tr. 215:20-23.) Defendants explained that they plan to present such evidence through expert testimony from Dr. Chodosh. (*Id.* 220:17-221:16.)

During the September 17 hearing, the Court offered to review portions of Dr. Chodosh's opinions to provide guidance regarding the extent to which Dr. Chodosh can testify about the "degree of risk" associated with ingesting valsartan containing NDMA or NDEA at the levels at issue. (9/17/24 Hr'g Tr. 134:24-135:9.) As the Court has recognized, and as discussed below, evidence of the risk of valsartan containing NDMA or NDEA is essential to the jury's evaluation of whether Plaintiffs received the benefit of the bargain, the central question for assessing

Plaintiffs' breach of warranty claims in many jurisdictions.

Defendants Are Entitled to Rebut Plaintiffs' Theory that These Are "Worthless Cancer-Causing Drugs"

As the Court recognized, in jurisdictions where breach of warranty is assessed based on whether the plaintiff received the benefit of the bargain, Defendants must be able to introduce evidence of the value of valsartan containing NDMA and NDEA. (*See, e.g.*, 9/17/24 Hr'g Tr. 114:13-115:3.) The Court observed, "the minute the plaintiff stands up and intuits to the jury that these are cancer-causing drugs and they have a zero value, I have now deprived the defendants of a fair trial, because they should be permitted to introduce evidence that they aren't cancer causing." (*Id.*) The Court further observed that if "the defendants stand up and they say there was value to these drugs. It lowered blood pressure, lowered blood pressure, et cetera, et cetera, and then the big elephant in the room is, uhmm, but what were the risks? And then I send a jury out to deliberate and they're like, uhmm, but what was the risk? They mentioned 'carcinogen.'" (*Id.* 123:12-18.) As the Court therefore recognized, the jury must be given a reliable evidentiary framework to gauge the risk and guidance on how to apply it.

The question for the jury in *this* trial is not whether the medication presented an "acceptable" or "unacceptable" risk; rather it is a question of whether the risk, if any, coupled with its undisputed efficacy, rendered the medication worthless. FDA decides what level of risk is "acceptable" to be on the market, while patients and their physicians decide what level of risk is "acceptable" to an individualized patient. Neither of these questions is within the scope of this trial, however. The jury's job here is to consider the risk-related evidence – whether from regulatory pronouncements relied upon by Plaintiffs or scientific expert opinion relied upon by Defendants – and decide its impact on worth. Both sides should be given a fair and balanced opportunity to contribute relevant evidence on the issue.[1]

As highlighted during the September 17 hearing, Plaintiffs' deposition designations illustrate that Plaintiffs want to have their cake and eat it too. Plaintiffs' designations are replete with testimony regarding cancer causation—despite

[1] This approach should not, however, result in any significant lengthening of the trial, given Defendants' previously provided estimate of Dr. Chodosh's testimony is merely one hour, and Defendants are reserving their full cadre of general causation experts, including their genetic toxicologist and epidemiologist, given the Court's direction so far.

Plaintiffs' counsel's representation to the Court that "[w]e're not going to say they caused cancer to people. That will never be said. In fact, we've been cutting our designations and taking out anything that smacks of general causation." (*Id.* 117:15-18.) Following this pronouncement, the Court requested of defense counsel, "I don't know. I have to see -- I have to see the depositions. If there are any that you're concerned about, flag them." (*Id.* 135:1-3.)

As a few examples of such designations, Plaintiffs have designated testimony from Teva's in-house toxicologist, Dr. Raphael Nudelman, for the sole purpose of introducing references to cancer and the carcinogenic classification of the impurities:

> Q. Okay. And **NDMA is classified as a probable human carcinogen; is that correct?**
>
> A. It is classified as a probable carcinogen based on animal studies. No human data is available.

(4/8/21 Deposition of Raphael Nudelman, Ph.D., ERT 61:9-19 (emphasis added).)

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> Q. . . . . **NDMA is a Class 1 impurity, a mutagenic carcinogen**, and according to the ICH M7 needs to have a compound-specific limit, which is the 0.182 micrograms per day." That's what you told her, in response to getting the health assessment draft, right?
>
> A. That's correct.

(*Id.* 179:13-180:12 (emphasis added).)

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> Q. Okay. So Siyu Liu, who is a medical doctor, says, **"I cannot say cancer is a temporary or medically reversible event."** And then she says, she talks about, "The risk level we talked about during our meeting; however, no data is available on **how many patients would get cancer** if they are exposed to higher level. **It could be a few patients per 100,000. We do not have the number."** Do you see that, sir?

A. Yeah, I see that. And I--

(*Id.* 190:2-14 (emphases added).)

Q. And then you say, "**NDMA is a potent carcinogen** with a TD50 value of 0.182 milligrams per kilograms per day which upon extrapolation gives a compound-specific acceptable limit of 0.182 micrograms per day. highest dose of valsartan 320 milligrams, this calculates to 0.57 parts per million. "In summary, the limit that NDMA needs to be controlled in valsartan." That's what you wrote, right?

A. Yes. Yes.

(*Id.* 159:19-160:9 (emphases added).)

Plaintiffs have also designated similar, cumulative testimony, including from witnesses who had no role whatsoever in evaluating toxicological impact, such as Mr. Karlsson, whose only involvement is on the commercial side of API procurement and simply researched NDMA online:

Q. I'm not asking you for a -- for you to do a toxicologist analysis. I'm just saying, Mr. Karlsson, did you understand at the time that NDMA could be toxic to certain human organs?

A. I can't recollect.

Q. You don't recollect. **Do you recall whether you learned that NDMA could be a suspected human carcinogen**?

A. I cannot recollect.

(3/18/21 Deposition of Stefan Karlsson 140:2-18 (emphasis added) (objections omitted).)

Q. And then you also wrote, "Based on what I could find online, the impurity, n-nitrosodimethylamine, is toxic and a known carcinogen for humans." Did I read that right?

> A. Yes.
>
> Q. So on your own initiative, you did research and you concluded and shared with your colleagues that **NDMA is toxic and a known carcinogen for humans, right**?
>
> A. I cannot remember what online source I reviewed to reach that conclusion. But, again, I'm not a toxicologist.

(*Id.* 146:16-147:10 (emphasis added) (objections omitted).)

The same type of testimony is designated for Teva quality assurance witnesses and witnesses testifying about testing methods. (*See, e.g.*, 4/14/21 Deposition of Daniel Barreto 140:2-18 ("Q. And she noted that the impurity was NDMA and it's defined as a probable human carcinogen, yes? A. Yes. That's what she indicated, yes.") (objections omitted); 5/13/21 Deposition of Anthony Binsol 80:12-18.) ("Q. It says, "NDMA is a semivolatile organic chemical that forms in both industrial and natural processes. It is a member of n-nitrosamines, a family of potent carcinogens." Did I read that right? A. You did.").)

Similar testimony is also designated for several Torrent witnesses, where Plaintiffs repeatedly asked witnesses to read or confirm language from publications and consultant reports that identify NDMA as causing tumor formation in lab rats, cancer-causing, genotoxic, and carcinogenic:

> Q. So on June 20, 2018, were you aware that **the only medical use of NDMA was actually to form tumors in lab rats**?
>
> A. No, I was not aware of that.

(5/13/2021 Deposition of Dawn Chitty 202:16-22 (emphasis added).)

> Q. And then we can see these news articles say, in the link it says the title, so it says "Europe recalls generic heart drug made in China on **cancer fears**." Do you see that?
>
> A. Yes.

(*Id.* 194:9-14 (emphasis added).)

> Q. All right. Looking at that paragraph, it says, "Based upon laboratory studies in which **tumors have been induced in all species examined at relatively low doses, NDMA is clearly carcinogenic**." Are you with me?
>
> A. Yes, reading here.

(6/4/2021 Deposition of Dr. Sushil Jaiswal 35:10-17 (emphasis added).)

> Q. Can we agree that the word **"carcinogenic" means can cause cancer**?
>
> A. Yeah. That is true. I agree with that.
>
> Q. All right. Let's look at the bottom of this paragraph where it says, "Qualitatively the metabolism of NDMA appears to be similar in humans and animals. As a result it is considered highly likely that **NDMA is carcinogenic to humans, potentially at relatively low levels of exposure**." Do you see that?
>
> A. Yeah, I read that.

(*Id.* 36:16-37:6 (emphasis added).)

> Q. On Page 5, paragraph on the left-hand side at the top, the last sentence says, "**NDMA is a genotoxic carcinogen**, and exposure should be reduced to the extent possible." Do you see that?
>
> A. Yes.

(*Id.* 41:11-17 (emphasis added).)

> Q. Okay. Take a look at the first sentence. Can you highlight that and then can you -- can you read that sentence aloud for me?
>
> A. Sure. "At very low concentrations (e.g. at the LOD) **the primary concern with chronic exposure to NDMA is a drug product with -- a drug product would be genotoxicity and carcinogenicity**."

(5/20/2021 Deposition of Bernadette Attinger 196:9-16 (emphasis added).)[2]

ZHP also previously flagged several examples of such designations from their witnesses for the Court. *See, e.g.*, 9/20/14 Ltr. from Jessica Davidson, Appendix A (ECF 2846).

This is by no means an exhaustive list of all the designated testimony from Defendants' witnesses related to the risk of **cancer**, specifically, associated with NDMA and NDMA in valsartan. It is evident that Plaintiffs cannot introduce evidence of the risk associated with NDMA or NDEA in valsartan without discussion of cancer and carcinogenicity. References to cancer and the alleged carcinogenicity of the at-issue medications are pervasive throughout the testimony Plaintiffs have designated for introduction at trial, and it is clear they intend to make this alleged risk a centerpiece of their trial presentation. Indeed, Plaintiffs' sole theory as to both causation and damages hinges on the presence of these impurities rendering the medications completely "worthless" due to the "unacceptable risk" allegedly posed to consumers from taking the drugs. Plaintiffs' assertion that their worthlessness theory is based solely on the regulatory recall is belied by their steadfast presentation of witness testimony squarely falling within general causation, such as "how many patients would get cancer?"

Dr. Chodosh's Testimony Refutes Plaintiffs' Worthlessness Theory

As detailed in his expert report, Dr. Chodosh assessed the risk posed by ingesting valsartan containing NDMA and NDEA "at the doses to which patients taking valsartan can -- potentially containing NDMA or NDEA would have been exposed and within the time frames to which they would potentially have been exposed."[3] (Deposition of Lewis A. Chodosh, M.D., Ph.D. (Sept. 29, 2001) ("9/29/01 Chodosh Dep.") 255:20-256:1.) He did so by analyzing the scientific

[2] Plaintiffs have also designated other testimony designed to elicit emotional reactions from jurors with respect to uses of NDMA: "Q. Is there something different between the NDMA that was found in Torrent's products and the **NDMA** that **used to be used as rocket fuel**? A. I don't know. Q. Did you inquire? A. No." (Attinger Dep. 193:23-194:4 (emphasis added).)

[3] Plaintiffs have never challenged Dr. Chodosh's qualifications or the reliability of his methodology under Rule 702, nor sought to preclude his proffered opinions in any way. Defendants reserve the right to present any and all opinions as fully set forth in Dr. Chodosh's expert reports and deposition, and this summary is in no way intended to limit or restrict Dr. Chodosh's opinions at trial.

literature on the levels of NDMA and NDEA in food, water, air, and other commonly ingested substances (exogenous exposures); the level of NDMA naturally produced within the human body (endogenous exposure); and the levels of exposure to NDMA and NDEA that have been shown to cause a detectable increase in tumor genesis in the most sensitive tissues of laboratory rodents. (Opinions of Lewis A. Chodosh, M.D., Ph.D. (Aug. 2, 2021) ("Chodosh Report") ¶¶ 81-98; 107-112.)

He also calculated and analyzed the maximum hypothetical levels of exposure of any individual patient to NDMA or NDEA from ingestion of any combination of valsartan products on the market containing these substances. (*Id.* ¶¶ 131-141; *see also, e.g.*, 9/29/01 Chodosh Dep. 304:4-16; 305:21-306:11.) He then compared the maximum hypothetical ingestion of NDMA and NDEA through valsartan to the levels of NDMA and NDEA in other exogenous sources, naturally produced endogenously, and known to cause cancer in experimental animals. (*See, e.g.*, Chodosh Dep. 305:21-306:11; 344:23-345:8.) He explained in his deposition:

> [T]he calculations that I did had a number of different elements. One of those elements was to take the lowest dose of NDMA or NDEA that caused a detectable increase in tumor genesis in the rat in -- so the most sensitive species and in the most sensitive site in that species, look at that on a milligram per kilogram basis, both on a daily basis and a cumulative basis, to compare what the maximum theoretical levels of exposure were of a human being to these compounds [via ingestion of valsartan] relative to that.

(9/29/01 Chodosh Dep. 305:21-306:11.) He further explained that he calculated and compared:

> the maximum theoretical exposure is under the most unlucky of conditions for a patient and compared that to what we know biologically about what we are all exposed to every day for both exogenous in diet and endogenous reasons, as well as the dosages at which cancers have ever been demonstrated to be caused by those compounds.

(*Id.* 344:23-345:7.)

Based on his analysis, Dr. Chodosh concluded, in part:

> The **maximum theoretical total amount of NDMA** to which any Plaintiff might conceivably have been **exposed through valsartan** is approximately **1,000-times lower than the amounts of NDMA produced endogenously**. Moreover, the maximum theoretical total amounts of NDMA and NDEA to which any Plaintiff might conceivably have been **exposed through valsartan** are **approximately 2,000- and 9,000-times lower**, respectively, **than the lowest doses shown to cause cancer in animal studies**.

(Chodosh Report at 63 (emphases added).)[4] Given those conclusions, Dr. Chodosh explained during his deposition why he did not calculate a "maximum safe dose" of NDMA or NDEA:

> Q. In your work regarding this case did you determine what the maximum safe dose level would be?
>
> A. In my report I did not determine the maximum safe dose. What I determined was that the maximum theoretical exposure of a patient to NDMA or NDEA, as a consequence of ingesting valsartan tablets containing those compounds, would have been **orders of magnitude lower than the lowest dose ever shown to cause cancer in a laboratory animal or to the endogenous levels** that are produced in our bodies, **so by definition I would consider that to be safe**.

(9/29/01 Chodosh Dep. 304:4-16 (emphasis added).) Plaintiffs' counsel pressed Dr. Chodosh on why he did not determine "what increased risk there was" as a result of the presence of NDMA and NDEA in valsartan, and he explained that it is because it is not biologically plausible that the maximum levels that were detected in valsartan could cause cancer:

> Q. As an expert that's offering the opinion that the doses in valsartan of NDMA cannot cause cancer in

[4] Dr. Chodosh's reference to "any Plaintiff" also means "any person," as he calculated and based his opinions on the time periods that products containing NDMA and NDEA were available on the market, not any particular individual's period of consumption. (*See, e.g.*, Chodosh Report ¶¶ 132-142.)

> humans, would it be important for you to determine what increased risk there was as a result of the contamination?
>
> A. No, it is the goal is to **determine is it plausible biologically that such an exposure could cause cancer**? And the **answer to that is resoundingly no**, it is not biologically plausible, given that you're talking about doses that have never been shown by anyone, under any context that I am aware of, to cause cancer in any type of animal.

(*Id.* 327:3-15 (emphases added).)

Dr. Chodosh also contextualized the FDA's acceptable daily intake (ADI) of NDMA and NDEA in pharmaceuticals. For example, he explained in regard to the FDA ADI of 96 nanograms per day of NDMA:

> Q. And that equates to a lifetime maximum cumulative exposure of 2,454 micrograms?
>
> A. From ingestion of pharmaceutical products, as opposed to the **larger amount of NDMA to which someone would have been exposed by eating and drinking and breathing**, not to mention the **endogenous levels of exposure that are orders of magnitude greater than that**. So this is specifically referring to a regulatory acceptable limit.

(*Id.* 342:8-24 (emphases added).)

Dr. Chodosh also explained the FDA's conservative estimates of the risk of cancer that may be associated with exposure to NDMA or NDEA in valsartan are based on linear low dose extrapolation from animal studies, which presumes that extremely low doses of a substance are potentially carcinogenic over the course of a human lifetime based on extrapolation from the extremely high doses observed to increase tumor rates in experimental animals. (*See, e.g.*, Chodosh Report ¶ 144.) Dr. Chodosh clarified that this approach may make sense from the perspective of a regulator but does not make sense from a biological perspective:

> So you're talking about regulatory issues for calculating safe doses, which is not my domain, other than to say for

> genotoxic carcinogens the FDA guidance on their -- with a safety mandate is to use linear low dose extrapolation, which assumes **effectively that one molecule of an agent will increase the risk of cancer**, whereas, to my recollection, nongenotoxic carcinogens are considered to have thresholds and, of course, the suitability from a biological perspective of the assumption by FDA, essentially that linear low dose extrapolation is biologically accurate at the exceedingly low doses that are at issue in this litigation, I think **most scientists, cancer biologists would say that** that is – those are overly conservative assumptions which are appropriate for a safety mandate of the FDA, but **from the biological perspective of causation, they do not make biological sense**.

(9/29/01 Chodosh Dep. 350:3-21 (emphasis added).)

Relatedly, Dr. Chodosh explained why (consistent with the Court's thoughts) dose is an essential element to a discussion of the potential risk of ingestion of NDMA and NDEA:

> Q. But in the case when the DNA damage is not repaired, that provides for the opportunity for cancer to form, correct?
>
> A. That is correct but that is **exactly the reason why dose is an absolutely essential element of the discussion** of the potential carcinogenicity in human beings and that the actual exposures in human beings and **the actual exposures at issue in this litigation are so small, so many orders of magnitude smaller** than what is to be considered here and very likely or **almost certainly smaller than endogenous exposures**, **the expectation is that damage that might occur at that level would be fully repaired**.

(*Id.* 270:20-271:9 (emphases added).)

Plaintiffs' counsel has represented that "you are not going to hear anybody say causation. All you're going to hear is the language that the FDA used and the

defendants used, which is that it was an unacceptable risk. And that's what witness after witness admitted in the testimony." (9/17/24 Hr'g Tr. 123:21-24.) But the FDA also said, "[p]atients taking the recalled valsartan-containing medicines should continue taking their medicine until they have a replacement product" because "the risks of stopping taking an ARB product for treating high blood pressure and heart failure greatly outweighs the potential risk of exposure from trace amounts of nitrosamines." *See* FDA "Statement on the agency's ongoing efforts to resolve safety issue with ARB medications" (August 28, 2019). So even if counsel's representation is accepted—Plaintiffs' designations notwithstanding—the jury needs further guidance as to how to reconcile the FDA's various pronouncements. And importantly, as Dr. Chodosh explained during his deposition and will explain to the jury at trial, there is a difference between a regulatory assessment of what is an "acceptable" risk to be sold on the market and what actually poses a risk of cancer, from the perspective of a cancer biologist. (9/29/21 Chodosh Dep. 308:19-310:3; 327:3-16-328:14.)

Defendants do not intend to make general causation the centerpiece of this trial and acknowledge that the jury does not need to render a verdict that valsartan at issue either does or does not cause cancer as a standalone element of Plaintiffs' claims. Plaintiffs' damages theory, however, does require the jury to balance the risks and benefits of the product in assessing its value and whether the Plaintiffs received the benefit of the bargain. Defendants will be gravely prejudiced if not allowed to respond to Plaintiffs' chorus of "unacceptable risk" with evidence and argument, which was never challenged at the Rule 702 stage, to explain the risk is actually *nil* from a scientific perspective. Any other result deprives the jury of the evidentiary framework needed to assess whether the mere presence of NDMA/NDA stripped valsartan of its worth.

We appreciate the Court's consideration of these issues and look forward to discussing further.

Sincerely,

/s/ Victoria Davis Lockard
Victoria Davis Lockard, Esq.

cc: All counsel of record (via ECf)